112 by the Examiner in the Final Action, but claim 8 is indicated as being allowable in the same Final Action. Therefore, it appears that the Examiner intended to reject claim 8 in the Final Rejection. For purposes of this Reply, the Applicants assume that claim 8 stands rejected under Section 112.

## II. The Section 112, Second Paragraph Rejection of Claim 8

The Examiner rejected claim 8 under 35 U.S.C. section 112. first and second paragraphs.

Applicants, without necessarily being in agreement with the rejections made by the Examiner have followed the Examiner's suggestions for this claim and have amended the term "$A_{2A}$" to read "$A_{2B}$". Applicants do not agree with the Examiner's suggestion that "neurotransmitter" be changed to "adenosine". If one were to make this change, then this portion of claim 8 would make no sense. There are 4 subtypes of adenosine receptors. One of those subtypes is the $A_{2B}$ receptor. If one were to make the suggested change, then the phrase would imply that 'adenosine antagonist mediated adenosine secretion'.

## III. The 35 U.S.C. 103(a) Rejection of Claims 4-6, 12-19 and 22

The Examiner has maintained his rejection of claims 4-6, 12-19, and 22 under 35 U.S.C. 103(a) as being obvious in view of EP 386683.

Applicants have reviewed the '683 publication. For the following reasons Applicants do not believe that any of claims 4-6, 12-19 and 22 is obvious in view of the '683 publication.

If one looks at the '683 publication, one sees a reaction scheme at the bottom of page 2, an example spanning pages 4 and 5, and Table 4 listing similar compounds on page 5.

The reaction scheme on page 2 of '683 teaches that a compound of formula IV (a 1-substituted 5,6-diaminouracil) is reacted with formic acid ($HCO_2H$) in the presence of base to yield a compound of formula I. If a person skilled in the art wanted to use the reaction scheme on page 2 of '683 to prepare compounds with a substituent in the 8-position of the xanthine ring, one would have to use a substituted carboxylic acid

($RCO_2H$) in place of formic acid. For example, if one wanted to prepare a xanthine compound with an N-pyrrolidinyl ring in the 8-position, one would have to use N-pyrrolidine carboxylic acid in place of formic acid. Even if N-pyrrolidine carboxylic acid existed, it would decarboxylate instead of closing the ring to form a xanthine compound.

The example spanning pages 4 and 5 teaches the preparation of 3-cyclopropylmethylxanthine (a compound of formula I wherein the only substituent is a methylcyclopropyl group in the 3-position of the xanthine ring . This example is specific to the preparation of a xanthine that is unsubstituted in the 8-position. For the reasons given above in the discussion of the reaction scheme on page 2 one could not use the example spanning pages 4 and 5 and expect to obtain a xanthine with a substituent in the 8-position.

Table 4 on page 5 lists compounds that can be prepared "by similar procedures". However, in Table 4, compound Ic does not have a melting point and compound Id indicates that it have just a nitrogen atom as a substituent in the 8-position of the xanthine ring. Since there is no characterizing data provided for compound Ic, a person skilled in the art could not prepare the compound with the substituents listed for compound Ic and have any certainty that he prepared compound Ic. Also, since there is just a nitrogen atom in the 8-position of the xanthine ring for compound Id, a person skilled in the art would not know which compound gives a melting point of 142 143°C.

For the reason that there is no teaching in '683 of how to make xanthines substituted in the 8-position, much less substituted by nitrogen-bearing entities. Applicants respectfully ask the Examiner to reconsider his obviousness rejection.

In addition to the above reason, Applicants also believe that the '683 publication is not an appropriate basis for an obviousness rejection because there is no definition for what a "$C_4$-$C_6$ aliphatic cyclic amino residue having one or more nitrogen atoms directly linked to the xanthine imidazole ring" is, nor are there any examples of compounds complying with this phrase.

The Examiner has also mentioned the Declaration filed by Applicants in reply to the Office Action of September 24. 2001. Applicants believe that, in view of the fact that the '683 document is not an appropriate basis for an obviousness rejection, a discussion of the Declaration filed by the Applicants is moot.

## IV. General Comments on Claims

### Claim 4

Applicants have amended claim 4 to make it independent. As described below, Applicants believe that the compounds of this invention are not obvious in view of the art cited by the Examiner. If the compounds are novel, pharmaceutical compositions comprising those compounds are novel.

In amending claim 4, Applicants have reinstated the term "cycloaliphatic amine group" as the definition for R. Applicants believe that they can be their own lexicographer. The term "cycloaliphatic amine group" is defined on page 10, lines 14-18, where it is stated to preferably be a secondary amine group. If the Examiner feels that there is another term for this R group, Applicants would welcome the suggestion.

### Claims 5, 6,7, 8,9, 10, 12, 19, and 22

In amending claims 5, 6,7, 8,9, 10, 12, 19, and 22, Applicants removed the term "unsubstituted" from the phrase "unsubstituted piperidino". Applicants believe that both substituted and unsubstituted piperidino groups are patentable over the references cited by the Examiner.

## V. Comments on New Claims

### Claim 24

Applicants have added independent compound claim 24. This claim finds support in the application as originally filed. Applicants believe this claim is patentable for the reasons given above in response to the 35 U.S.C. 103(a) rejection.

In the September 24, 2001 Office Action the Examiner also rejected claims under 35 U.S.C. 103(a) as being unpatentable over Bonte (U.S. Patent 5,470,579). In that Office Action the Examiner pointed out that compounds in '579 belong to the same species as applicants have, except that it has the extra methyl at the 1-position. In that Office Action the Examiner went on to state that one of ordinary skill in the art expects secondary and tertiary amines to have generally similar properties.

Applicants respectfully point out that '579 sets forth a generic formula. To come up with a specific compound one would have to pick and choose from a very large list of

alternative substituents. In column 2, lines 22-24, the '579 patent lists one of the alternatives for $R_4$ as where $R_6$ and $R_7$ "form together, with the nitrogen atom, a heterocycle, preferably a saturated monocyclic heterocycle". There is no definition for either heterocycle or monocyclic heterocycle. In column 2, lines 34-51 there is a list of compounds. The only alternative listed for $R_4$ that could be construed as a heterocycle is piperidin-1-yl. In addition there is no teaching of how to make a piperidin-1-yl containing compound. In column 4 Bonte states that the compounds can be synthesized, obtained commercially, or are plant extracts. There is no indication as to which means a person would use to obtain a piperidin-1-yl substituted xanthine. The only examples in '579 are for use of 3- or 1-substituted xanthines. If the compound is one that is synthesized, one would have to hunt among the references listed (but not incorporated by reference) to find if one taught a method for preparing a xanthine with $R_4$ being piperidin-1-yl. In addition, the compounds of '579 are listed as useful for promoting pigmentation in skin or hair. One of ordinary skill would not look to the pigmentation art for direction for discovering selective $A_{2B}$ antagonists. They are not analogous arts.

For these reasons Applicants believe that claim 24 is patentable over the '579 patent.

**Claim 25**

Applicants have added independent claim 25. This claim finds support in the application as originally filed. Applicants believe this claim is patentable for the following reasons.

In a September 24, 2001, Office Action the Examiner rejected a claim directed to a method of treating inflammatory diseases under the first paragraph of section 112 for containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make or use the invention.

The examiner stated:

> "Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by

> which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally."

Applicants respectfully direct the Examiner's attention to the following points. Inflammation is described in Goodman and Gilman's The Pharmacological Basis of Therapeutics (1996. Eds. Hardman, Limbird, Molinoff, Ruddon, and Gilman. McGraw Hill. NY. p618-619) as the following:

> "The inflammatory process involves a series of events that can be elicited by numerous stimuli (*e.g.*, infections agents, ischemia, antigen-antibody interactions, and thermal or physical injury). Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation on a theme. At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain. Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms: (1) an acute transient phase, characterized by local vasodilatation and increased capillary permeability; (2) a delayed subacute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells; and (3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur. Many different mechanisms are involved in the inflammatory process (Gallin *et al.*, 1992; Kelly *et al.*, 1993). The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury, although in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reason.

Thus, although etiologic factors and tissues vary, an inflammatory response is basically the same regardless of the tissue. Inflammation is the culmination of a series of biological events and whatever the initiating event the steps are the same. Drugs have been developed to inhibit various steps of the inflammatory response and these drugs have been used in many different types of inflammatory disorders. Thus, steroids have been used in pulmonary inflammation caused by asthma, in rheumatoid arthritis, multiple sclerosis, glomerulonephritis; cyclosporin is used to inhibit the growth of T-cells in many inflammatory disorders including Behcet's syndrome, uveitis, atopic dermatitis, psorasis, rheumatoid arthritis, Crohn's disease and biliary cirrhosis.

For these reasons Applicants believe that a claim directed to a method for treating inflammatory diseases is an allowable claim.

**Claim 26**

Applicants have added independent claim 25. This claim finds support in the application as originally filed. Applicants believe this claim is patentable for the following reasons.

In the September 24, 2001 Office Action the Examiner rejected a claim similar to new claim 26 because of the use of the term "cardiac disease" which he contended, "simply means any disease of the heart". In that Office Action the Examiner appeared to be suggesting that the specification does not supply enablement for a broad range of cardiological diseases. In claim 26 the Applicants have amended the claim to further elucidate the invention. The Applicants believe that claim 26 is patentable.

The Examiner has not given any reasons why he believes that the specification is not enabling for a claim directed to a method of treating cardiac disease. The specification, in fact, provides a list of indications covering a wide variety of disease states. The diseases are linked because they are mediated by adenosine $A_{2B}$ receptors. In cardiovascular tissues, for example, $A_{2B}$ receptors mediate contractility and consequently, are modulating tensive states. $A_{2B}$ receptors also regulate the activity of vascular smooth muscle cells further modulating blood flow to the heart. Thus, agents that regulate the activity of $A_{2B}$ have utility as therapeutic modalities in diseases mediated by activity of the $A_{2B}$ receptor. The use of the compounds as $A_{2B}$ receptor antagonists is fully described in Example 2 on p. 16.

Applicants respectfully submit that the assertions of usefulness for the compounds of the invention are straightforward and believable on their face. The compounds of the invention have been found to be adenosine $A_{2B}$ antagonists. Compounds with such utility are known to be useful for the claimed methods of treatment (Example 2, p.16, for example).

## VI. The Allowability of all Pending Applicati n Claims

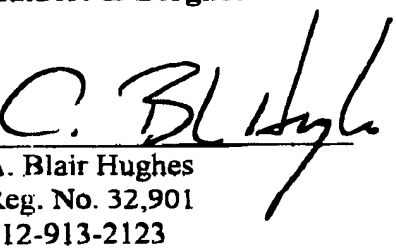
Claims 4-10, 12-19, and 22-26 are pending as a result of this Reply. In view of the above amendments and arguments, Applicants believe that all of pending claims are allowable and that all rejections and objections should be withdrawn.

Applicants request the Examiner to reconsider the rejections in view of the above arguments and claim amendments. Favorable reconsideration and allowance of the pending application claims is therefore courteously solicited.

Respectfully submitted,

**McDonnell Boehnen Hulbert & Berghoff**

Dated: September 18, 2002

By: 

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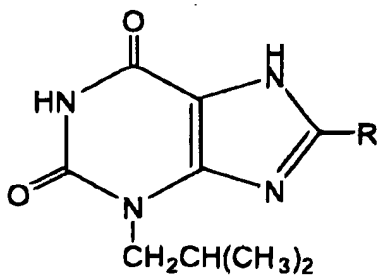
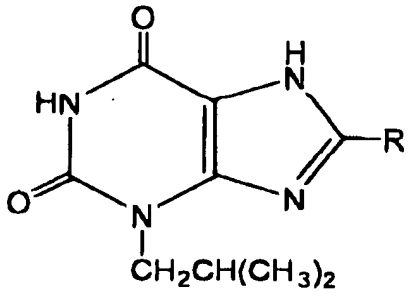
**Appendix A**
**Marked Up Claims Pursuant To 37 CFR 1.121**

4. (Twice amended) A pharmaceutical composition comprising a compound of [claim 23] the following formula:



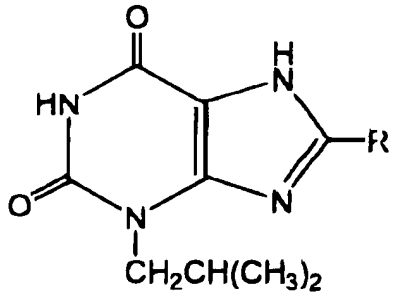
or a pharmaceutically acceptable salt thereof, wherein R is a cycloaliphatic amine group, and a pharmaceutically acceptable carrier.

5. (Twice amended) A method of antagonizing $A_{2B}$ receptors comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



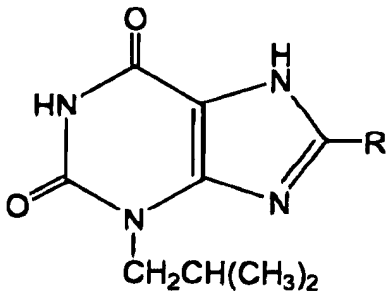
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

6. (Twice amended) A method of treating asthma comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



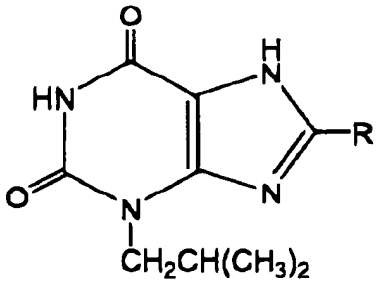

wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

7. (Twice amended) A method of treating diarrhea comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



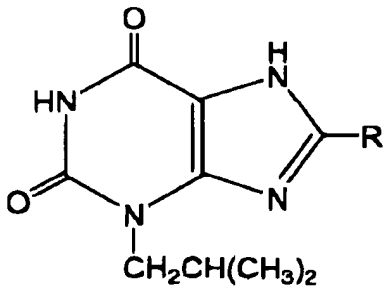

wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

8. (Twice amended) A method of regulating at least one of smooth muscle tone, blood vessel growth, and [$A_{2A}$] $\underline{A_{2B}}$ antagonist mediated neurotransmitter secretion comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



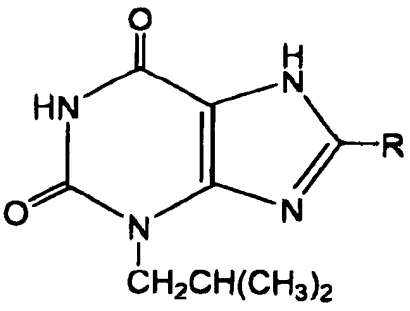
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

9. (Twice amended) A method of treating inflammatory gastrointestinal tract disorders comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



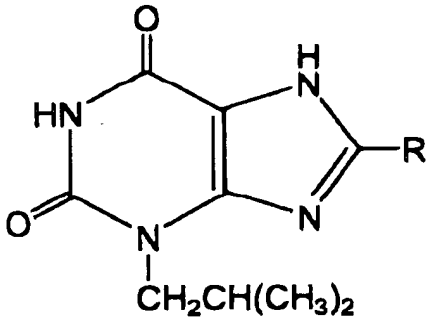
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

10. (Twice amended) A method of treating depression comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



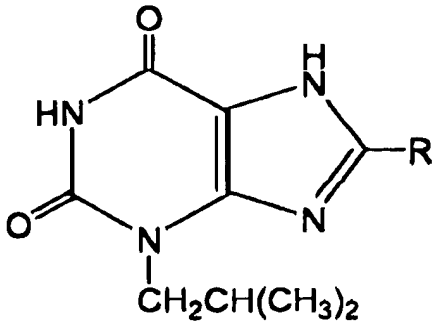
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

12. (Twice amended) A method treating a disease selected from the group consisting of: arthritis, asthma, multiple sclerosis, septic shock, endotoxic shock, gram



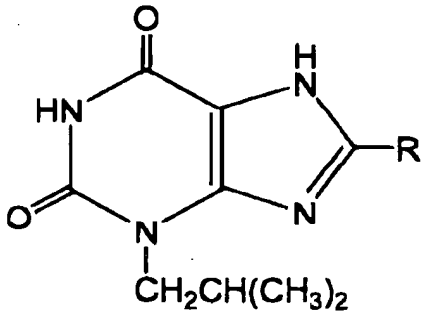

negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, organ transplant rejection, cachexia secondary to cancer, osteoporosis, infertility from endometriosis, bacterial meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment comprising administering to a mammal in need thereof, an effective amount of a compound of the following formula:
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

19. (Twice amended) A method of modulating human mast cell function comprising administering to a patient in need thereof an effective amount of a compound of the following formula:



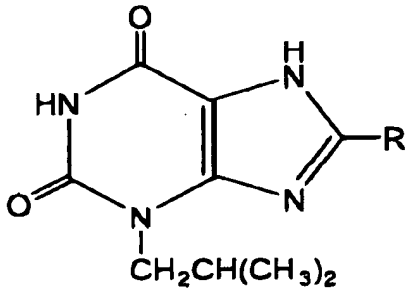
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

22. (Once amended) A compound of the following formula:



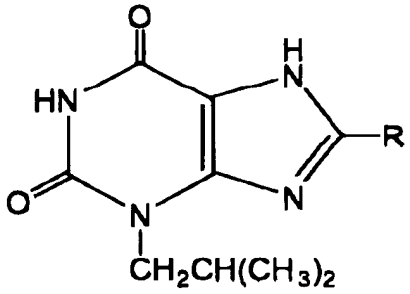
wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, [unsubstituted] piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

24. (New) A compound of the following formula:



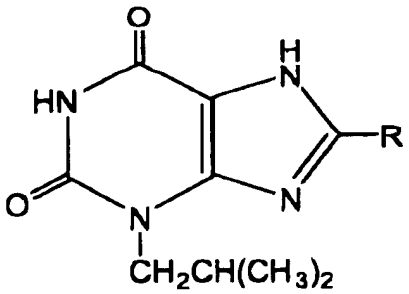

or a pharmaceutically acceptable salt thereof, wherein R is cycloaliphatic amine.

25. (New) A method of treating inflammatory diseases, comprising administering to a mammal in need thereof an effective amount of a compound of the formula:




wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.

26. A method of treating cardiac diseases that are mediated by $A_{2B}$ receptors comprising administering to a patient in need thereof an effective amount of a compound of the formula:




wherein R is selected from $C_1$ to $C_6$ alkyl amine, $C_1$ to $C_6$ dialkyl amine, piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof.